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XIII INTERNATIONAL CONGRESS OF INTERNAL MEDICINE, HELSINKI, FINLAND, 15-19 AUGUST 1976

CDR Michael Stek, MC, USN, NMRI*

14 JANUARY 1977

*National Naval Medical Center, Bethesda, MD

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Ths conference was divided into several main sessions focused on the role of bile acids in slinical medicine and iatrogenic disease. These were combined with parallel and free paper (which unfortunately overlapped) devoted to a wide range of subjects in internal medicine. Sessions of particular interest dealt with infectious disease and clinical immunology.

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XIII INTERNATIONAL CONGRESS OF INTERNAL MEDICINE
HELSINKI, FINLAND, 15-19 AUGUST 1976

Introduction

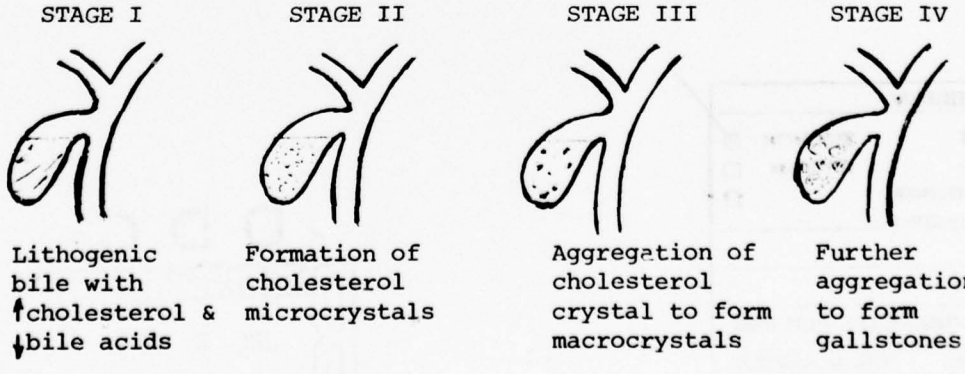
On 15-19 August 1976 the XIII International Congress of Internal Medicine was held in Helsinki, Finland, organized by the Finnish Society of Internal Medicine for the International Society of Internal Medicine. The conference was divided into several main sessions. Papers on the role of bile acids and estrogenic disease are reviewed in this report. Reviews of parallel sessions and free papers dealing with infectious disease and clinical immunology are also reported. The Congress offered a unique opportunity to hear and meet with a vast number of clinicians and researchers in the broad scope of internal medicine from throughout the world.

Bile acids in gallstone disease

H. Dowling, U.K. (Gastroenterology Units, Guy's Hospital, London)

Cholesterol recirculates primarily via the enterohepatic circulation, but some is eliminated as bile acids and neutral steroids in the stool. Bile acid was at one time considered basically a single entity, however, various papers presented at the opening session of the Congress point out that there are a number of bile acids with varying effects. For example, Dr. H. Dowling described how chenodeoxycholic acid (CDCA) acts effectively to dissolve gallstones. His discussion was confined to cholesterol rich gallstones (i.e., those with greater than 70% cholesterol). Although a number of other treatments have been attempted for the dissolution of gallstones, CDCA appears the most promising at the present time.

The following is an illustration of the sequence of events leading to gallstone formation:



Treatment with CDCA increases the concentration of CDCA in the bile acid pool which causes a feedback inhibition of HMG CoA-reductase thus retarding hepatic cholesterol formation and subsequently reducing biliary cholesterol secretion. This leads to an unsaturated bile in respect to cholesterol, and cholesterol-rich stones present in the gall bladder begin to dissolve. Dowling reported on the treatment of 41 patients for periods of greater than 6 months: 17 were found to have complete resolution of gallstones, 3 had partial resolution and 21 had no change. Obesity was noted to be correlated with poor patient response. In addition, more rapid and complete resolution occurred more frequently as the size of the initial stones were reduced. The most suitable patient for CDCA therapy (15 mg/kg/d) was found to be the non-obese individual with small radiolucent gallstones.

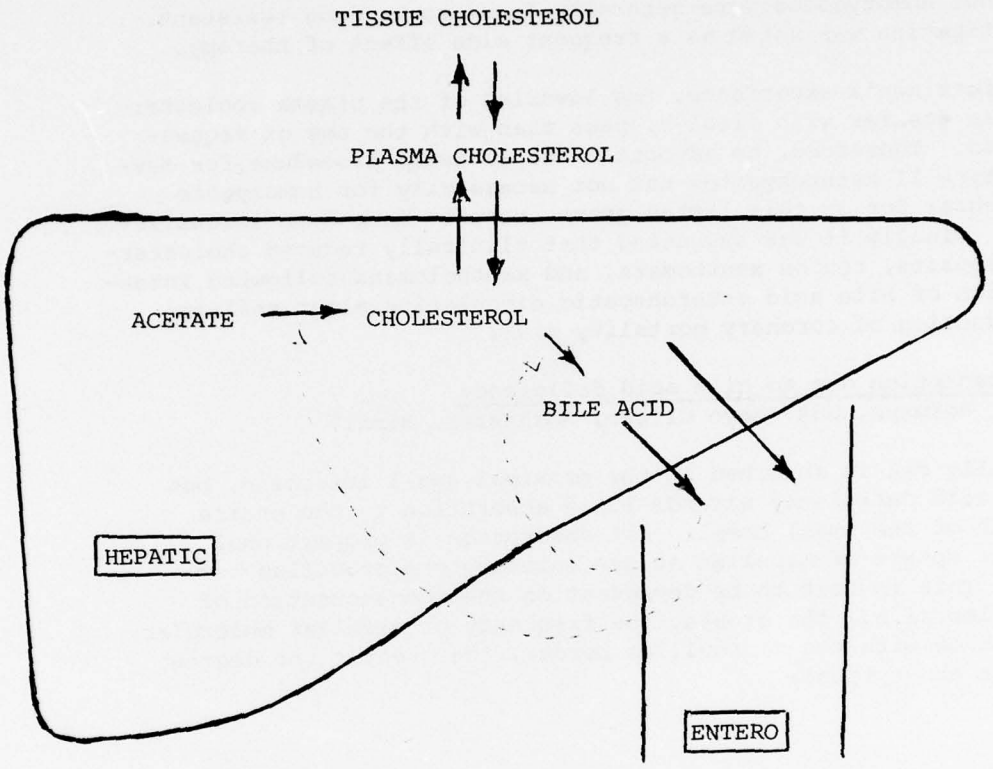
A distinct drawback, however, of CDCA therapy is that once treatment is discontinued it has been found that the bile returns to a super-saturated state with high levels of cholesterol in approximately 1-3 weeks. In fact, Dowling noted that of the 17 patients with complete resolution of gallstones, within an average of one year of CDCA therapy, five developed recurrences. Thus, if CDCA is to be used, long term treatment should be considered.

Treatment of hyperlipidermias with bile acid sequestrants and ileal exclusion

T. A. Miettinen, Finland (Second Dept. of Med. U. Helsinki)

During his discussion of bile acid sequestrants and ileal by-pass treatment of hyperlipidemias, Dr. T. A. Miettinen presented better results with the Buchwald ileal-by-pass procedure than recorded in most US studies. This may be attributed to the length of ileum excluded (i.e., 1/2 of the terminal ileum or 2 m, whichever is longer).

Bile acid sequestrants and ileal exclusion interrupt the normal bile acid eutero-hepatic circulation by increasing fecal bile acid elimination which ultimately acts to lower plasma cholesterol.



Entero-hepatic circulation

Miettinen found three bile acid sequestrants to be effective particularly for type IIA hyperlipidemia and occasionally for type IIB. The following results were presented as average laboratory data changes noted in patients:

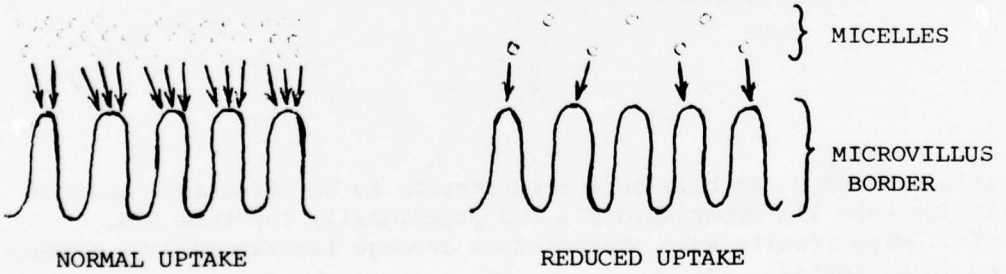
	CHOLESTYRAMINE	COLESTIPOL	DEAE-SEPHADEX
Plasma Cholesterol	-24	-26	-21
Plasma Methyl Sterols	+131	+165	+152
Fecal Bile Acids	+311	+424	+219
Fecal Total Steroids	+65	+131	+52

Type II subjects, including xanthomatotic hypercholesterolemic heterozygotes experienced 10-35% reduction in plasma cholesterol, but homozygotes were generally found to be drug resistant. Constipation was noted as a frequent side effect of therapy.

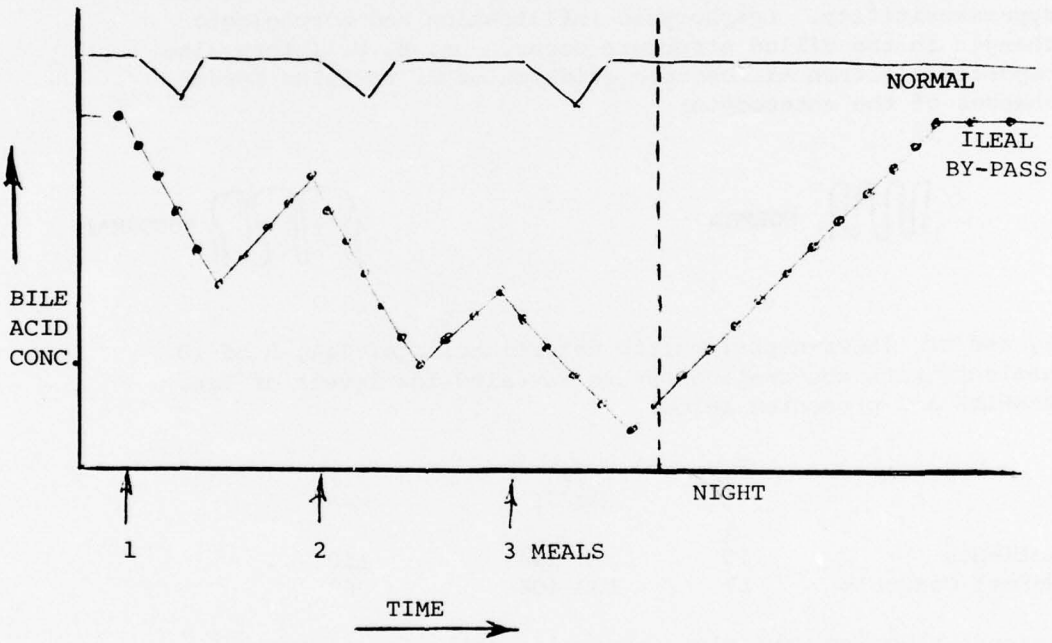
In Miettinen's experience, the lowering of the plasma cholesterol was greater with ileal-by-pass than with the use of sequestrants. Therefore, he advocates the Buchwald procedure for severe type II heterozygotes but not necessarily for homozygote patients; for in this latter group, results have been inconsistent. Finally it was suggested that clinically reduced cholesterol deposits, tendon xanthomata, and xantholomata following interruption of bile acid enterohepatic circulation might reflect a reduction of coronary mortality risk.

Malabsorption due to bile acid deficiency
A. F. Hofmann, USA (Mayo Clinic, Rochester, Minn.)

Normally fat is absorbed in the proximal small intestine, but bile acid deficiency extends lipid absorption to the entire length of the small bowel. Fat absorption is proportional to the uptake of micelles at the enterocyte microvillus border. This is felt to be dependent on the concenctration of micelles (i.e., the greater the frequency of micellar molecular collision with the microvillus border, the greater the degree of fat absorption):



Patients with total biliary obstruction or fistulae present defective micellar solubilization because of lowered bile acid levels. In patients with ileal-by-pass, the bile acid concentration was found to decrease throughout the day with marked falls following meals. Recovery of bile acid concentration occurs during the night. Normal fluctuation of bile acid occurred with meals as well, but recovery was prompt. The following diagram depicts those changes:



Maldigestion coupled with a decreased anatomical reserve may lead to steatorrhea. Cholestyramine causes fat maldigestion, but probably because of a normal anatomical reserve, steatorrhea is generally mild.

Hofmann recommended reduction of fat intake for the treatment of bile-acid-deficiency impaired micellar solubilization. This was shown to reduce fecal weight and frequency of stools. Water soluble fatty acid substitutes in the diet (i.e., C8-C12) was suggested as possible non-cathartic replacements not dependent on micelles for absorption.

Immunological studies on patients with idiopathic sprue
H. W. Intorp, FRG (Medizinische U. Poliklinik, Münster)

Non-tropical sprue is small bowel malabsorption due to gluten hypersensitivity. Lymphocytic infiltration and morphologic changes in the villus structure occur. Dr. H. W. Intorp also reported electron microscopic evidence of microvillus border changes of the enterocyte:

By use of laser-nephelometric determination of IgA, 8 of 10 patients with non-tropical spure revealed low levels of IgA. Results are presented below:

	#	IgA mg/dl	Mean
Patients	10	74-144	110
Normal Controls	57	102-406	268

Jejunal biopsies were also obtained. Utilizing fluorescein conjugated antisera against IgA, M, and G respectively, Intorp noted a reduction in IgA producing cells, however, an increase in the number of cells producing IgM and G were noted when compared with normal controls. The following ratios were reported:

	IgA :	IgM :	IgG
Non-tropical Spure	31%	61%	8%
Normal Controls	59%	35%	6%

The high incidence of HLA8 histocompatibility antigen noted in a number of patients with non-tropical spure by Intorp further suggests an immunologic disorder.

(1) The role of viruses in systemic lupus erythematosus (SLE)
(2) Type C oncornavirus studies in SLE, I. Attempted detection of ^{3}H-uridine labeled virus.
(3) Type C oncornavirus studies in SLE II. Attempted detection of viral RNA-directed DNA polymerase (RDDP)
P. E. Phillips, USA (Hosp. Special Surgery, New York)

The New Zealand mouse disease offers a model for SLE where type C oncornavirus is involved. LE cells are formed and ANA Antigen-antibody deposits with glomerulonephritis have been found in kidneys as well. Autoimmune hemolytic anemia also develops in these mice. The disease is under genetic control and endogenous type C virus has been demonstrated. It was suggested that canine SLE might also be viral induced. The following hypothetical sequence of events leading to SLE was offered by Phillips.

(1) Vertically transmitted (cell to daughter cell) type C virus
(2) Genetic predisposition
(3) Virus replication in T-cells
(4) T-cell destruction
(5) Decreased cell- mediated immunity
(6) Increased viral expression
(7) Increased antibody response
(8) Circulating immune complexes
(9) Inflammatory reaction to cell viral antigens
(10) Multi-system disease (SLE)

Phillips noted that Mellors (1976) utilizing indirect immunofluroescence reported finding type C viral antigens in human SLE kidney and spleen. Using radio immune assay, Phillips reported that he could not confirm Mellor's findings.

Viral-like particles (tubuloreticular inclusions) first thought to be associated with SLE tissues was shown by Phillips to be present also in normal placental tissue. In addition, his viral isolation

studies have been negative. Phillips contended, therefore, that the rise of viral antibodies found in SLE may be a nonspecific reaction to increased antibody mediated immunity.

For detection of ^{3}H-uridine labeled virus, Phillips used Type C sedimentation at 1.16 g/ml density. Eleven studies were conducted on cells from 1 discoid LE and 7 SLE patients, three placenta, two blood leukocyte, two spleen, one kidney, and one synovium cells were placed in culture and maintained for up to 18 months. Iododeoxyuridine was used to treat culture sets. Unlabeled replicate culture sets were negative for viral RNA-directed DNA polymerase and for viral particles by electromicroscopy. Transmission of an SLE peak or DEAE dextran treated rabbit and mink cells was equivocal. Phillips did not consider that the 1.16 g/ml peaks which occurred were type C viral but were due to RNA containing organelles released from disrupted radiolabeled cells. This conclusion appears to be begging the issue.

Following this discussion, Phillips presented data on 33 experiments o on tissue cultures, and frozen tissue samples from 13 definite and 6 possible SLE patients, 9 placenta, 3 spleen, 2 synovia, 1 kidney, 1 thymus, and 1 skin biopsy were cultured up to 16 months. Induction was with iododeoxyuridine. The medium was harvested monthly and tested for type C viral RDDP. Murine Type C virus (+) controls typically incorporated approximately 1000-pM 3H-TMP/ml, while negative controls incorporated less than 0.2 pM/ml. Thirteen of 724 SLE samples tested were greater than 10 pM/ml. Six of these were from mouse cells with probable type C contamination. The other 7 positives were from frozen SLE spleen innoculated on H-NRK cells (non-viral producing rat cells). The virus banded at 1.16 g/ml but would not grow in other cells, and was not transforming. Phillips concluded that the virus was probably not Type C but another in H-NRK cells. If this were true, he should have been able to demonstrate the virus in other H-NRK cultures; however, he was unable to do this. It may be that in the transcribed state a relative state of viral dormancy exists which might account for Phillips' failure to identify active virus or products.

Antibiotic induced disorders

H. Otten, FRG (Institut für chemotherap. Bayer AG)

The increased use of antibiotics have caused a growth in the incidence of side effects (toxic, idiosyncratic, allergic, and superinfection or reinfection). Approximately 20-25% of all drug reactions are related to antibictics which places them as the most frequent cause of drug reaction. The following data was offered to illustrate a number of antibiotics and specific sites of reactions:

Site of Reaction	PCN	AMP	CEPH	AG	TETRA	CHLOR
Skin	75	20	30	5	45	10
GI	8	20	45	10	25	30
Kidney	1	1	10	30	5	1
Blood	4	2	5	5	5	45
Other	12	8	10	50	20	15

(Frequency recorded above in upper % limit)

PCN = penicillin
AMP = ampicillin
CEPH = cephalosporin
AG = aminoglycoside
TETRA = tetracycline
CHLOR = chloramphenicol

Iatrogenic factors and malignant disease

D. B. Clayson, USA (Eppley Cancer Inst. Omaha, Neb.)

Case reports, retrospective and prospective, epidemiologic studies have led to the implication of the carcinogenic effects of certain drugs. For example, estrogens utilized to maintain pregnancy have been shown to induce vaginal clear cell adenocarcinoma in female progeny.

More recently oral contraceptives and androgens have been implicated as a cause of benign hepatic tumors. This may be of particular note when oral contraceptives are used regularly and over an extended period of time. Of those acquiring the tumor about 10% die secondary to hemorrhage.

Considering the seriousness of the tumor, Clayson suggested the establishment of an international registry to monitor and collect epidemiologic data to confirm or deny the clinical impression.

Drug-related liver diseases
Sheila Sherlock, U.K. (Royal Free Hosp, London)

Dr. Sheila Sherlock contended that the previous classification of drug-related liver disease should be replaced by new categories.

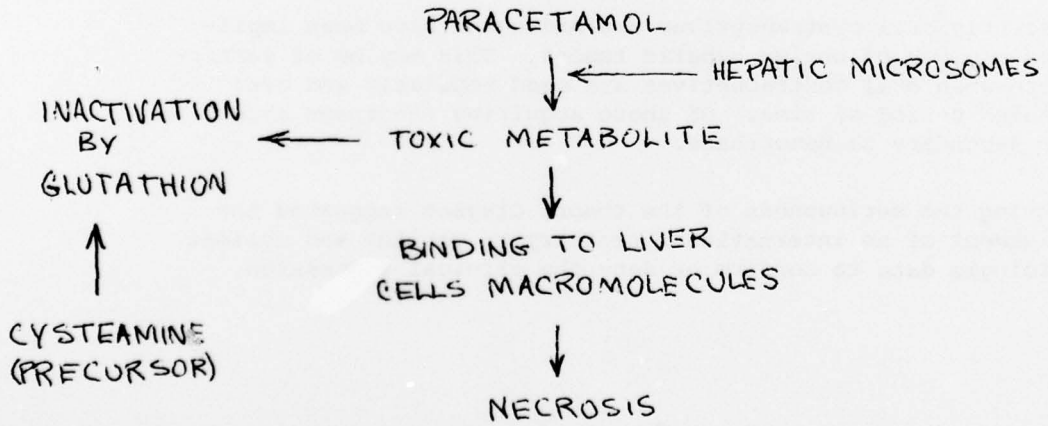
Previous System

(1) Dose-dependent--predictable
(2) Dose-independent--non-predictable

Present System

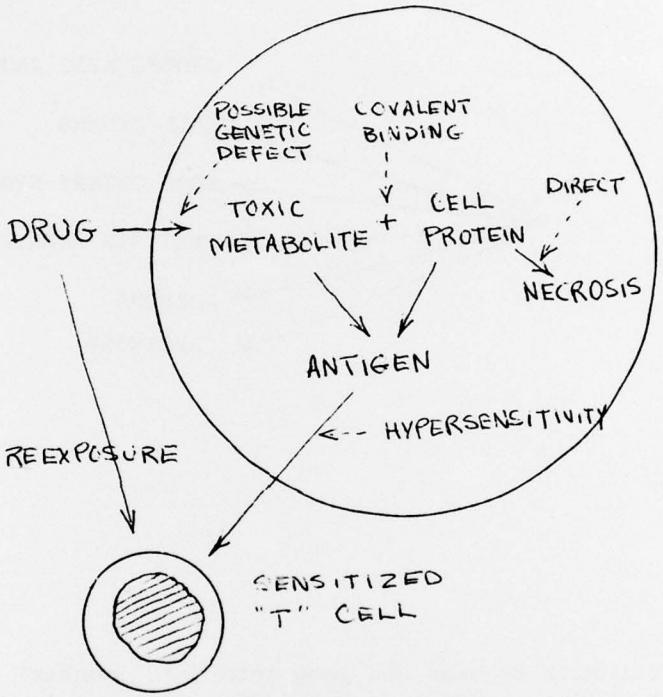
Type	Drug Examples
(1) Direct	Tetracycline
(2) Metabolite related	Paracetamol (Tylenol)
	Isoniazid
	Methyl DOPA
	Halothane
(3) Hypersensitivity	Sulphonamides
	Nitro-furantoin
(4) Canalicular cholestasis	17 Alpha-alkyl steroids
	Methyl Testosterone
	Arsenicals
(5) Hepatic fibrosis & Angio sarcoma	Arsenicals
	Vinyl chloride
(6) Adenoma & Carcinoma	Contraceptives
(7) Gallstones	Contraceptives

The sequence in metabolic related disease may be illustrated below with paracetamol:



Therefore, if cysteamine is given to a tylenol overdose patient within the first 12 hours, the degree of hepatotoxicity should be reduced.

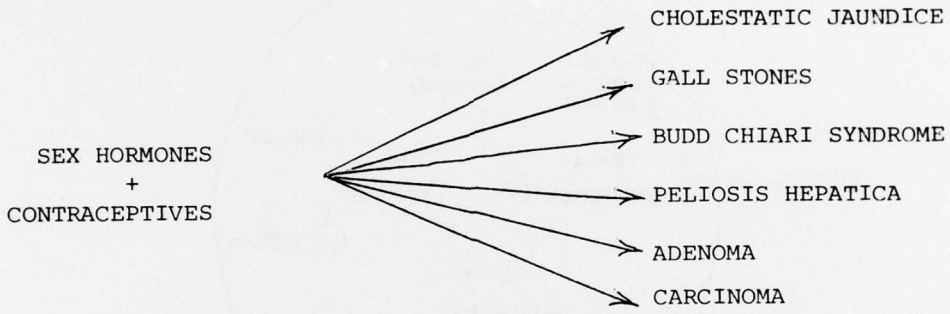
Sherlock presented the following schematized version of how hepatotoxicity may occur:



A suggestion was made that rifampicin reported hepatitis may not be due to rifampicin but to INH, with rifampicin acting as an inducer, rather the reverse of the situation where PAS acts as a reducer of INH related hepatitis.

Of the hypersensitivity group, the incidence is reported to be generally low, tends to occur with repeated use of the drug and is independent of the dosage utilized. Phenothiazines, sulphonomides (septrin should be watched carefully), nitrofurantoin, anti-thyroid drugs, diphenylhydantoin, and erthromycin isolate (not recommended for use) may lead to hypersensitivity induced drug jaundice.

The sex hormones and contraceptives have recently caused concern and should be more throughly evaluated.



Increased risks occur with regular and long term (>100 months) use. Adenomas which readily hemorrhage occur 25 times more frequently than in controls not utilizing birth control pills.

Bacterial endocarditis

L. R. Freedman, Switzerland (Univ. Lausanne)

Studies of the pathogenesis and the effect of therapy of bacterial endocarditis have been limited because of the lack of an appropriate laboratory model. Freedman reported on his method of producing bacterial endocarditis in a number of animals (notably in the rabbit). An indwelling polyethylene catheter or steel

wire was inserted via the venous or arterial system to permit the tip of the catheter or wire to rest in the heart cavity in which endocarditis was to be produced. Following intravenous injection of an inoculum of bacteria, endocarditis was regularly produced. The infecting dose, however, varied with the organism:

E. coli			XXXXX
Strep. viridans		XXXXX	
Staph. aureus	XXXXX		
	10^3	10^5	10^7

This experimental model appeared closely to resemble human bacterial endocarditis. The injections were usually characterized by bacteremia, anemia, splenomegoly, emboli myocarditis, and pulmonary arteritis (in right heart infections).

Histologically, the vegetations were composed of masses of interwoven fibrin in which microcolonies of bacteria were formed to be imbedded. Scanning electron micrographs were shown which revealed a tight matrix which would barely permit the entrance of an erythnocyte but would almost certainly exclude the larger leukocytes. Thus a physical explanation was established which could explain the sparse numbers of leukocytes detected in conventional biopsy material.

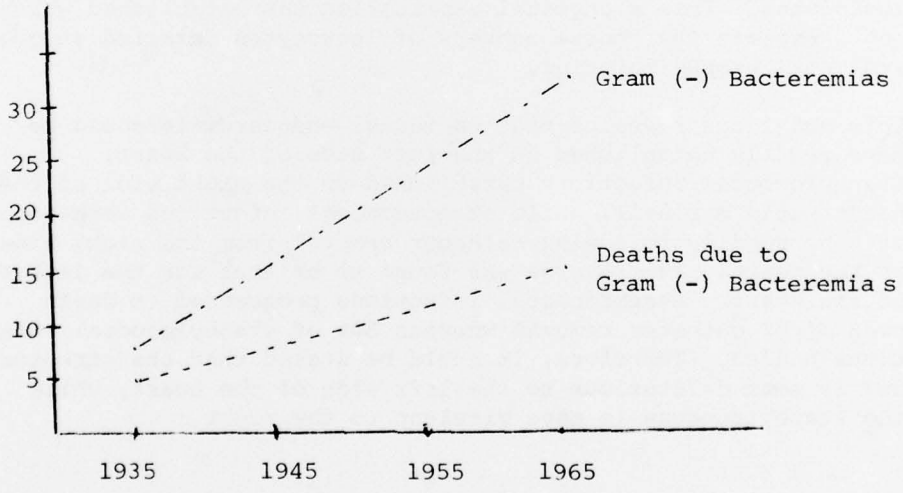
This model has revealed that bacterial endocarditis could be more readily established on the left side of the heart. Staphylococcal infections established on the right side of the heart would not heal, while streptococcal infections were found to heal readily following catheter removal from the right side of the heart. The reverse was found to be true for the left side of the heart. Streptococcal infections progressed to death even after catheter removal whereas 50% of staphylococcal infections healed. Therefore, it could be stated that the streptococcus is more deleterious to the left side of the heart, while the staphylococcus is more virulent to the right.

Further, the model pointed to the difficulty encountered with penicillin prophylaxsis and supported the value of penicillin-aminoglycoside synergism for the prophylaxsis and treatment of *Streptococcus viridans* and the treatment of *Staphylococcus aureus* infections, suggesting that the present American Heart Association recommendation of penicillin prophylaxsis may not be enough.

Pathogenesis and management of bacteremia

E. H. Kass, USA (Channing Laboratory, Harvard Medical School, Boston

Although there has been a general fall in communicable dis eases during the last 40 years, intrahospital Gram-negative bacteremias have shown dramatic increases such that Kass would now consider the situation in epidemic terms. Data from Boston City Hosp. for 1935 to 1965 were presented to illustrate this.



A number of other centers have also reported increases in the numbers of deaths secondary to Gram-negative bactermias. However, a number of smaller hospitals have reported far less Gram-negative bacteremia, which Kass contends might be due to under-reporting. Or might it be that there has been less Gram-negative infections introduced to these hospitals and less nosocomical disease. The general frequencies for bacteremias range from 0.5-2.0%). Kass felt that a busy general hospital would be expected to have a frequency of about 2.0% and suspected that lower figures might often be due to an insufficient number of blood cultures.

Kass reported that at Boston the urinary tract accounted for most of the Gram-negative bacteremias and that careful attention to the detection and eradication of urinary infections should substantially reduce the incidence.

Summarizing the literature on bacteremias, Kass presented the following table:

SOURCES OF BACTERIA IN FATAL CASES OF BACTEREMIAS

	%
Urinary tract	65
Skin	14
Gastrointestinal track	10
Respiratory tract	3
Subdiaphram abscess	1
Undetermined	7
	100

Ample proof now exists that the primary problem is that of the indwelling catheter. The use of closed systems, antimicrobial rinses, and frequent changes of the catheter would reduce the incidence of bacteremias and the death rates. However, as Kass pointed out, this simple fact is still quite poorly accepted or not at all.

A similar situation exists with intravenous catheters. Kass presented data indicating that the use of an antibiotic ointment at the site of catheter entrance significantly reduced bacteremia.

	Antibiotic	Placebo
# Patients with catheters	201	207
(+) Blood cultures	25 (12%)	65 (31%)

In addition, he recommended IV catheter replacement every 3 days

Further, Kass contended that analyses for endotoxin-like substances such as the limulus test may not be routinely employed to estimate progress at this time because of the number of false negatives which might be obtained.

Kass presented evidence that resistance of bacteria to various antibiotics might vary significantly from place to place. For example, a high degree of staphylococcal resistance has been reported from Copenhagen but has been rarely seen in Stockholm. Therefore, antibiotic application must be individualized to the particular situation. The use of steroids continues to remain debatable. A good control study with high dose initial steroid use is needed. Kass concluded that the best treatment for Gram-negative bacteremia is prevention.

The teichoic acid antibody test in patients with congulase positive staphylococcal bacteremia

Ulla M. Rikkonen, M. V. Valtonen, M. Sanvas, and V. V. Valtonen, Finland (Central Public Health Laboratory and U. of Helsinki)

Rikkonen ***et al*** **employed** the gel diffusion technique of teichoic acid antibody (TAA) detection and in addition compared these results with antistaphylolysin (ASTA) determination. A poor correlation between these two tests was noted, which is not surprising, for the ASTA often has poor reliability.

Positive titres of 1:2 - 1:16 generally appeared 1 week after the onset of symptoms. The following results were reported:

	#	% TAA(+)
Staphylococcus aureus coagulase pos.	47	60
Staphylococcus aureus coagulase neg.	6	0
Other bacteremias	61	10
Normal controls	74	0

The highest titres were obtained from endocarditis patients:

	#	0-1:1 TAA(-)	1:2-1:4 (+)	1:8-1:16 (++)
SAC (+) Endocarditis	6	0	2	4

Teichoic acid antibody formation and metastatic abscesses in patients with staphylococcus bacteremia

C. U. Tuazon, M. S. Choa, D. Marcus, J. A. Curtin, and J. N. Sheagren, USA (George Washington U. Washington, D.C.)

The teichoic acid antibody (TAA) analysis may prove to be an acceptable method of serologic evaluation of *Staphylococcus aureus* coagulase positive (SAC(+)) infections. Tuazon *et al*, reported on TAA by countercurrent immunoelectrophoresis (CIE) which appears to be more sensitive than simple gel diffusion. The data suggests tha TAA may be of value in determining the presence of metastatic complications of SAC(+) infections. Fourteen of 26 patients with SAC(+) blood cultures were shown to be TAA(+). Of these, 50% were shown to have metastatic foci such as arthritis, empyema, osteomyelitis, and urinary infection. Only one of the 12 patients negative for TAA revealed a metastatic focus (urinary infection). Actually in these instances the urinary infection may have preceded the bacteremia. SAC(+) endocarditis was not included in this study.

Since TAA becomes positive relatively early in the course of illness, its appearance may have potential value as a prognostic indicator of metastatic spread. And since TAA tends to fall with resolution of disease, it may also be potentially useful as a guide to when therapy should be discontinued.

Virological aspects of acute and chronic hepatitis

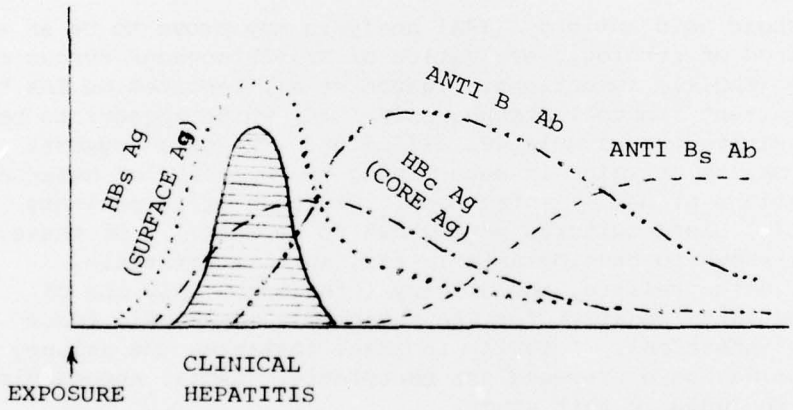
A. J. Zuckerman, UK (London School of Hygiene and Tropical Medicine)

Three distinct antigen-antibody reactions occur in man infected with hepatitis B infection:

1. Surface antigen: HB_s Ag-Ab: adw, adr, ayw, ayr
2. Core antigen : HB_c Ag-Ab
3. eAg : eAg-Ab

The last may prove to be highly significant, for it appears to correlate well with progression to chronic liver damage.

The appearance of antibody to the first two antigens in relation to clinical disease was illustrated with the following graph:



Hepatitis B vaccines are presently being developed. Krugman has shown in human volunteers that heated (+) sera could be used as a "vaccine" which offers a degree of protection. Zuckerman cautioned, however, that care would have to be exercised not to include host DNA in the active vaccines. An approach which offers promise is the use of Hepatitis B viral polypeptides free of host and viral DNA.

"Epstein-Barr' virus (EBV), infectious mononucleosis, Burkitt's lymphoma, and nasopharyngial carcinoma
G. Klein, Sweden (Karolinska Inst., Stockholm)

Burkitt first described the lymphomia which bears his name as related to the hot humid environment of tropical Africa and postulated an insect vector for this tumor which he felt was of viral origin. Indeed, the EBV has since been found in the majority of African Burkitt's lymphoma patients tested (97%) but is relatively rare in patients outside of Africa (5%). The virus has also been found in cells of nasopharyngial carcinoma, primarily in patients of southern Chinese decent. The EBV is associated with infectious mononucleosis but may cause no symptoms at all.

Klein has found that the EBV, a lympho-tropic herpes-like virus, can transform B cells into blasts and thence to an "immortal" cell line which continues to carry the viral gene. The EBV B-cell receptor sites appear to be related to the complement receptor sites, for co-capping was shown by Klein to occur. However, co-capping was not noted when EBV was compared with immunoglobulin receptor sites.

Interferon and its clinical applications
K. Cantell, Finland, (Central Public Health Laboratory Helsinki)

Interferon is a protein that can be produced by most vertebrate cells. It has been shown to inhibit viral replication, cell division, and intracellular microorganism growth. It can be stimulated into production by the use of inducers, but its concentration is generally low. Also, there has been a significant morbidity with

drug inducers. The alternative would be to use interferon produced from human cell lines *in vitro*. During the past 13 years, the Central Public Health laboratory in Helsinki has been working on the *in vitro* preparation of interferon. Cantell reported that approximately 10^{11} units of leukocyte interferon were produced last year in Finland in an improved purified and concetrated form of 10 million units/ml. He noted that if administered IV, the interferon was rapidly cleared from the circulation, but if given IM or SC, a moderately stable plateau could be maintained utilizing daily injections of 2-3 million units.

Human leukocyte inferferon is currently being evaluated in a number of clinical situations. Cantell reported on work by Jones soon to appear in *Lancet* utilizing interferon in herpes keratitis. More rapid improvement was noted, and a lower frequency of recurrences developed when an interferon ointment was compared to a placebo opthalomologic preparation:

	INTERFERON	PLACEBO
Patients	60	25
Reucrrences	6 (10%)	13 (52%)

$p < 0.01$

Cantell suggested that in hepatitis B, interferon may reduce the frequency of chronic hepatitis. Initial studies by T. C. Merigan have shown a fall in core antigen and, more interesting by, a fall in e antigen as well. Improvement was also noted in patients with *Varicella zoster* (T. C. Merigan *J. InF Dis* in press).

Preliminary data on interferon's use in osteosarcoma is also promising. Swedish studies have shown that prior to the introduction of interferon, 20% of osteosarcoma patients survived to 2 years with surgery and radiation. Present treatment with resection of the tumor (amputation or exarticulation) and 3 million units of interferon a day while in the hospital followed by 3 million units three times a week at home was compared with a historical control group.

No added benefit was considered from radiation. The following percentage survival graph was shown: